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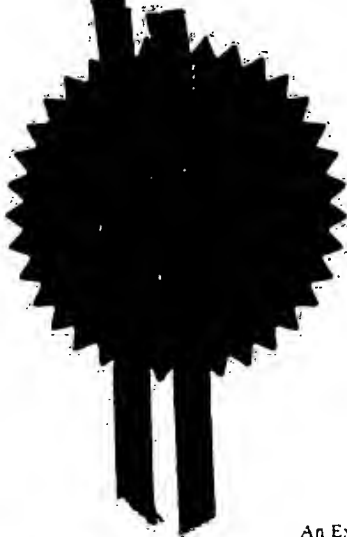
The Patent Office
Concept House
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South Wales
NP10 8QQ

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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

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Signed

Andrew Gersey

Dated 10 January 2000

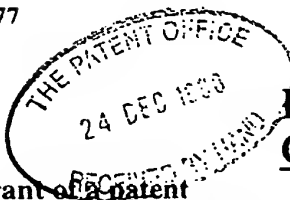
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ATTORNEY DOCKET NUMBER: 10589-012-999
SERIAL NUMBER: 10/543,033
REFERENCE: B10

Patents Form 1/77

Patents Act 1977
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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Cardiff Road
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1. Your reference	4-30759/P1		
2. Patent application number (The Patent Office will fill in this part)	9828707.1		
3. Full name, address and postcode of the or of each applicant (<u>underline all surnames</u>)	NOVARTIS AG Schwarzwaldallee 215 4058 Basel		
Patents ADP number (<i>if you know it</i>)	7125487002		
If the applicant is a corporate body, give the country/state of its incorporation	Switzerland		
4. Title of the invention	Pharmaceutical Uses		
5. Name of your agent (<i>if you have one</i>)	B. A. Yorke & Co.		
"Address for service" in the United Kingdom to which all correspondence should be sent (<i>including the postcode</i>)	Coomb House 7 St. John's Road Isleworth, Middlesex TW7 6NH		
Patents ADP number (<i>if you know it</i>)	1800001		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (<i>if you know it</i>) the or each application number	Country	Priority application number (<i>if you know it</i>)	Date of filing (<i>day / month / year</i>)
7. If this application is divided or otherwise derived from a earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (<i>day / month / year</i>)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer "Yes" if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))	Yes		

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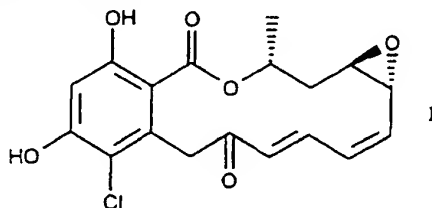
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PHARMACEUTICAL USES

This invention relates to radicicol and radicicol analogs and in particular to new pharmaceutical uses of such compounds.

Radicicol the compound of formula 1



has been known for many years as a natural compound, e.g. as a metabolite of the microorganism *Monosporium bonorden*, and was described initially as having antibiotic properties (Delmotte, Nature 171, 344 (1953)).

Novel Radicicol analogs, processes for their preparation and their pharmaceutical use are described in European patent application EP 0606044 A, together with known compounds including radicicol, O-methyl radicicol, and the related compound zearelenone and certain analogs of zearelenone. The radicicol analogs and known compounds are described in EP 0606044 A to be useful for the treatment of disorders with an aetiology associated with or comprising excessive cytokine release, particularly IL- β release, such as rheumatoid arthritis, osteoarthritis, septic shock, psoriasis, atherosclerosis, inflammatory bowel disease, Crohn's disease and asthma. The disclosure of EP 0606044 A is incorporated by reference in the teaching of the present application.

Surprisingly it has now been found that radicicol, radicicol analogs, zearelenone and zearelenone analogs (hereinafter collectively referred to as radicicol analogues), such as those described in EP 0606044 A, are useful for treatment of certain forms of cancer and malignant diseases.

Accordingly the present invention provides use of a radicicol analog for preparation of a medicament for treatment of a cancer and/or malignant disease.

4-30759/P1/GB

- 3 -

-d-e- is $-\text{CHR}_7-\text{CHR}_8-$ or cis or trans $-\text{CR}_7=\text{CR}_8-$.

wherein R_7 and R_8 are the same or different and are H, OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-, and

-f-g- is $-\text{CH}_2-\text{CH}_2-$, cis or trans $-\text{CH}=\text{CH}-$, or $-\text{C}(\text{O})-\text{CH}_2-$

and pharmaceutically acceptable salts thereof and physiologically-hydrolysable and -acceptable esters thereof.

The carbon atom marked with an asterisk (*) in formula II is an asymmetric carbon atom. The carbon atoms at a, b, c or d may also be asymmetric carbon atoms dependent upon the particular substituents present at these positions. Asymmetric carbon atoms at these positions may have the R- or S-configuration or the radical analog may comprise any mixture of the optical isomers thereof. Preferred isomers include those specifically described hereinafter.

Halogen or halo as used herein refers to F, Cl, Br or I unless otherwise indicated, preferably Cl.

A particular subset of the compounds of formula II for use in the invention are those in which one of -a-b- or -d-e- is $-\text{CHR}_7-\text{CHR}_8-$ and the other is cis- or trans- $-\text{CR}_7=\text{CR}_8-$, wherein R_7 and R_8 are the same or different and are H, OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-, and c is $>\text{CH}-\text{OH}$ or $>\text{C}=\text{O}$, and wherein R_1 , R_2 , R_3 and -f-g- are as defined above.

Preferred significances for the variable substituents and moieties of the radicalanalogs of formula II are as follows:

Preferably R_1 and R_3 are the same or different and are H, -OH, MeO- or Me-COO-. Preferably R_2 is -OH, MeO- or MeCOO-. More preferably R_1 is H or MeO; R_2 is MeO, and R_3 is OH or MeO.

Preferably -a-b- is cis- or trans- $-\text{CR}_7=\text{CR}_8-$, wherein R_7' and R_8' are the same or different and are H, OH, MeO- or Me-COO-. More preferably -a-b- is cis- or especially trans- $-\text{CH}=\text{CH}-$.

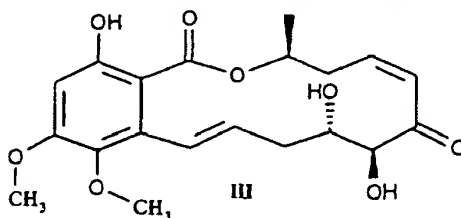
Preferably -d-e- is $-\text{CHR}_7'-\text{CHR}_8'-$, wherein R_7' and R_8' are as defined above. More preferably -d-e- is $-\text{CH}_2-\text{CH}_2-$ or especially $-\text{CHOH}-\text{CHOH}-$, wherein the OH groups may be in free or protected form.

4-30759/P1/GB

- 5 -

aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, an acidic -OH group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts.

EP 0606044 A describes the isolation and characterisation of the radicicol analog of formula III.

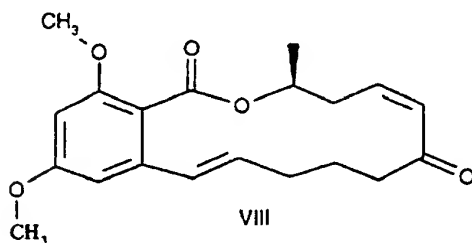
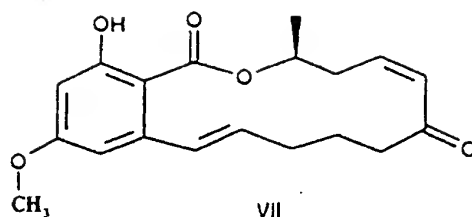


hereinafter referred to as radicicol analog A, which was first identified as a natural product isolated from a strain of pycnidia imperfect fungi (F/87-250904) deposited on 6 November 1991 with the ARS Patent Culture Collection, US Dept. of Agriculture, Northern Regional Research Centre, Peoria, Illinois, USA under the provisions of the Budapest Treaty as deposit NRRL 18919.

Radicicol analog A is a particularly preferred radicicol analog for use in the present invention. Radicicol analog A also serves as a valuable starting material for synthesis of other radicicol analogs for use in the present invention. Alternatively EP 0606044 A describes the de novo synthesis of radicicol analogs starting from readily available starting materials.

The disclosure of EP 0606044 relating to the isolation of radicicol analog A from the fungal strain F/87-250904, the synthesis of semi-synthetic radicicol analogs from radicicol analog A and the de novo synthesis of radicicol analogs, is specifically incorporated by reference in the teaching of the present application.

Particularly preferred radicicol analogs for use in the invention include compounds of formula II in which -a-b- is trans- -CH=CH-, e.g. the compounds of formulae IV, V and VI



The compounds for use in the invention have valuable pharmacological properties. In particular compounds for use in the invention have valuable properties as inducers of degradation of mRNAs which contain mRNA instability sequences. The activity of compounds for use in the invention as inducers of mRNA degradation may be demonstrated by means of a reporter gene assay as hereinafter described in the Examples, or as described in more detail in our copending British patent application, of even date herewith, entitled "ASSAY".

~~In view of their activity as inducers of degradation of mRNAs which contain mRNA instability~~ sequences, the radicicol analogues are useful for the prophylaxis and treatment of cancers and malignant diseases which involve inappropriate build-up and expression of mRNAs, which contain mRNA instability sequences, and which code for proteins involved in the initiation, progression or persistence of cancer or malignant disease. Examples of cancer related genes, with mRNAs which contain mRNA destabilising sequences, include various oncogenes and transcription factors, e.g. c-myc, c-fos, Spl, bcl-2 and similar genes. The inappropriate or prolonged expression of such oncogenes is implicated in the initiation of certain forms of cancer, such as colon cancer, breast cancer, lung cancer etc.. Further examples of cancer related genes, with mRNAs which contain mRNA instability sequences are genes for metalloproteinase enzymes, e.g. MMP-1, MMP-2, collagenases etc., involved in tissue remodelling required for tumour growth and metastasis invasion; cell cycle related genes such as p45/SKIP2 etc. and multidrug resistance genes, e.g. mdr-1, MRPs, etc. involved in the intrinsic or acquired multidrug resistance of some cancer cells.

inhibitor. The radicicol analogs exhibit inhibitory activity in the micromolar range, for example an IC_{50} of approximately from 0.1 to 10 mM, especially from 0.4 to 4 mM.

The radicicol analogs exhibit inhibition of the growth of tumour cells *also in vivo*, as shown, for example, by the test described below: the test is based on inhibition of the growth of the human epidermoid carcinoma A431 (ATCC No. CRL 1555; American Type Culture Collection, Rockville, Maryland, USA; see Santon, J.B., *et al.*, Cancer Research 46, 4701-4705 (1986) and Ozawa, S., *et al.*, Int. J. Cancer 40, 706-710 (1987)), which is transplanted into female BALB/c nude mice (Bomholtgard, Denmark). That carcinoma exhibits a growth that correlates with the extent of the expression of EGF-receptor. In the experiment, tumours having a volume of approximately 1 cm³ cultured *in vivo* are surgically removed from experimental animals under sterile conditions. The tumours are comminuted and suspended in 10 volumes (w/v) of phosphate-buffered saline. The suspension is injected s.c. (0.2 ml/mouse in phosphate-buffered saline) into the left flank of the animals. Alternatively, 1×10^6 cells from an *in vitro* culture can be injected in 0.2 ml of phosphate-buffered saline. Treatment with test compounds is started 5 or 7 days after the transplant, when the tumours have reached a diameter of 4-5 mm. The test compound in question is administered (in different doses for different animal groups) once a day for 15 successive days. The tumour growth is determined by measuring the diameter of the tumours along three axes that are perpendicular to each other. The tumour volumes are calculated using the known formula $p \times L \times D^2/6$ (see Evans, B.D., *et al.*, Brit. J. Cancer 45, 466-468 (1982)). The results are given as treatment/control percentages ($T/C \times 100 = T/C \%$). At a dose of from 3 to 50 mg/kg active ingredient, distinct inhibition of the tumour growth is found, for example T/C % values of less than 10, which indicates strong inhibition of tumour growth.

The radicicol analogs for use in the invention can be used both alone and in combination with other pharmacologically active compounds, for example together with inhibitors of the enzymes of polyamine synthesis, inhibitors of protein kinase C, inhibitors of other tyrosine kinases, cytokines, negative growth regulators, for example TGF- β or IFN- β , aromatase inhibitors, antioestrogens and/or cytostatic agents.

Characteristically when the radicicol analogs are used to prevent or reverse multidrug resistance of tumour and other malignant cells, they are used in combination with cytostatic or cytotoxic

Additional procedures for assessing utility in restoring sensitivity of cancer cells to anti-neoplastic/cytotoxic drug substances, including *in vivo* procedures are described in EP 0296122 B, the relevant disclosures of which are incorporated by reference in the teaching of the present application.

Suitable pharmaceutical compositions comprising radicicol analogs as active ingredient and that can be used especially in the treatment of the diseases mentioned above include compositions for enteral, such as nasal, buccal, rectal or especially oral, administration and parenteral, such as intravenous, intramuscular or subcutaneous, administration to warm-blooded animals, especially human beings. The compositions comprise the active ingredient on its own or preferably together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends on the disease to be treated, and on species, age, weight and individual condition, individual pharmacokinetic conditions, and the mode of administration.

The pharmaceutical compositions may comprise from approximately 1% to approximately 95 % active ingredient, forms of administration in single dose form preferably comprising from approximately 20 % to approximately 90 % active ingredient and forms of administration that are not in single dose form preferably comprising from approximately 5 % to approximately 20 % active ingredient. Unit dose forms are, for example, dragées, tablets, ampoules, vials, suppositories or capsules. Other forms of administration are, for example, ointments, creams, pastes, foams, tinctures, lipsticks, drops, sprays, dispersions, etc. Examples are capsules comprising from approximately 0.05 g to approximately 1.0 g of the active ingredient.

The pharmaceutical compositions are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising procedures.

Solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that contain the active ingredient alone or together with a carrier, for example mannitol, for such solutions, suspensions or dispersions to be made up prior to use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, for example by means

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, or alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Dragée cores can be provided with suitable, optionally enteric, coatings, there being used *inter alia* concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Orally administrable pharmaceutical compositions also include dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilisers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Other oral forms of administration are, for example, syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 5 % to 20 %, preferably about 10 %, or in a similar concentration that provides a suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example,

EXAMPLES

Example 1: Reporter Gene Assay for compounds which destabilise mRNA

A. Construction of pGL2_neo30

In order to obtain a vector for stable integration into THP-1 cells a XhoI - Sall fragment of the neo resistant gene derived from pMCIneo (Stratagene) is subcloned into the Sall site of pGL2-Control (Promega). A 30bp fragment obtained by annealing two complementary synthetic oligonucleotides (see Fig 1) is subcloned using the PflMI restriction site. This 30bp fragment contains three tandem AUUUA motifs based on the IL-1 β 3'UTR sequence. Modification of pGL2-Control (Promega) by introducing a neomycin resistant marker gene (expressing aminoglycoside 3' phosphotransferase) and by adding 30bp of IL-1 β 3'UTR sequence results in the luciferase expression vector pGL2_Neo30 (Fig. 2). Fig. 1 shows the IL-1 β 3'UTR sequence containing three tandem AUUUA motifs used for ligation into the PflMI site of pGL2Control.

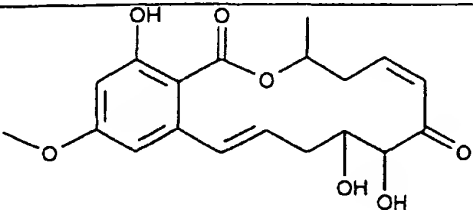
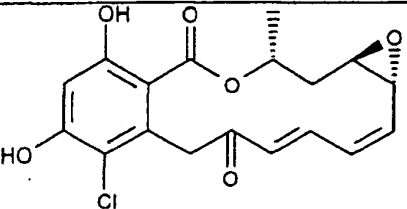
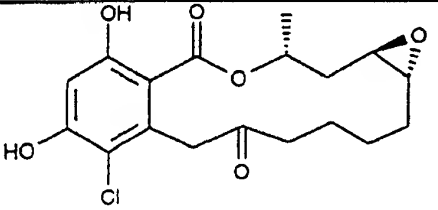
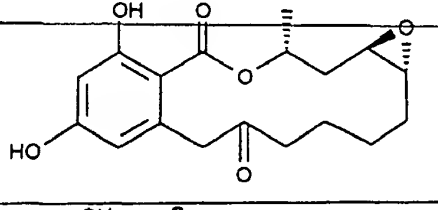
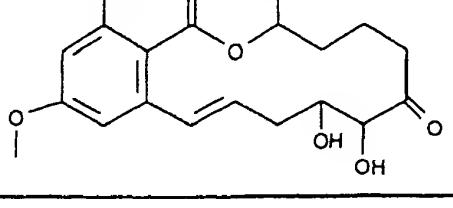
B. Transfection and selection of stable cell lines

The resulting vector (pGL2_neo30) is cotransfected with pGL2-Control into THP-1 cells by electroporation. 10^7 cells/ml in 1.3mM KH_2PO_4 , 7.36mM Na_2HPO_4 , 2.44mM KCl, 124mM NaCl, 5mM glucose, 9.6 μM MgCl_2 and 16 μM CaCl_2 pH 7.2 are transfected with 20 μg of DNA in a Bio-Rad Gene Pulser (250V, 690 μF and indefinite resistance) using a 0.4cm cuvette. Cells are subsequently cultured in RPMI medium containing 10%FBS, 2mM L-Gln, 50 μM 2mercaptoethanol and 600 $\mu\text{g}/\text{ml}$ of G418 (geneticin). After transfection of pGL2_Neo30 and pGL2-Control into THP-1 cells, stable cell lines are obtained by selection for G418 resistance and assayed for luciferase activity. One cell line of each transfection is chosen for further analysis; the pGL2_Neo30 cell line is referred to as clone No. 63 and the pGL2-Control cell line as clone No. 53. No endogenous luciferase activity could be detected in normal THP1 cells.

C. Tissue culture:

The transfected human monocytic leukemia cell lines, clones No. 53 and 63 are grown in RPMI medium supplemented with 110 U/ml penicillin, 100 $\mu\text{g}/\text{ml}$ streptomycin, 2 mM L-Gln (L-glutamine) and 2 g/l NaHCO_3 . Heat-treated FBS (5%) is added before use. The cells are grown to a density of $5 \times 10^5/\text{ml}$ and induced to differentiate with 100 U/ml (final concentration) IFN. Three

TABLE

<u>COMPOUND</u>	<u>Luciferase reporter gene assay</u>			
	clone	0.5 μ M	1 μ M	5 μ M
	53	114	105	107
	63	97	88	87
	53	68	51	40
	63	42	18	3
	53	99	77	69
	63	88	64	57
	53	83	81	70
	63	80	66	61
	53	103	122	104
	63	107	93	70

Example 5: Film-coated tablet, each comprising 100 mg of radicicol analog A or a pharmaceutically acceptable salt are prepared as follows:

Composition (for 1000 film-coated tablets)

active ingredient	100.0 g
lactose	100.0 g
corn starch	70.0 g
talc	60.0 g
calcium stearate	1.5 g
hydroxypropylmethylcellulose	2.36 g
shellac	0.64 g
water	q.s
methylene chloride	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened with a paste prepared from 15 g of corn starch and water (with heating) and granulated. The granules are dried, the remainder of the corn starch, the talcum and the calcium stearate are added and mixed with the granules. The mixture is compressed to form tablets (weight: 280 mg) which are then film-coated with a solution of the hydroxypropylmethylcellulose and the shellac in methylene chloride: final weight of the film-coated tablet: 283 mg.

Example 6: Hard gelatin capsules, comprising 100 mg of active ingredient, for example radicicol analog A or a pharmaceutically acceptable salt are prepared, for example, as follows:

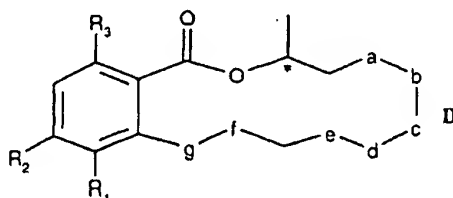
Composition (for 1000 capsules)

active ingredient	100.0 g
lactose	250.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is added to the lyophilised active ingredient through a sieve of 0.2 mm mesh size. The two components are intimately mixed. Then first the lactose is added through a

CLAIMS

1. Use of a radicicol analog for preparation of a medicament for treatment of a cancer and/or malignant disease.
2. A method for the prophylaxis or treatment of a cancer and/or malignant disease comprising administering to a patient an effective amount of a radicicol analog.
3. A use according to claim 1 or method according to claim 2 in which the radicicol analog is a compound of formula II



wherein

R_1 is H, OH, halogen, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-;

R_2 is OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-;

R_3 is H, OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-;

-a-b- is -CHR₇-CHR₈- or cis or trans -CR₇=CR₈-,

wherein R_7 and R_8 are the same or different and are H, OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-, or

-a-b- is -CHR₇-CHR₈- and R_7 and R_8 together with O form an epoxide bridge;

c is >CH-OH, >C=O or >CH₂;

-d-e- is -CHR₇-CHR₈- or cis or trans -CR₇=CR₈-,

wherein R_7 and R_8 are the same or different and are H, OH, C_1 - C_4 lower alkoxy, or C_1 - C_4 lower alkyl-COO-, and

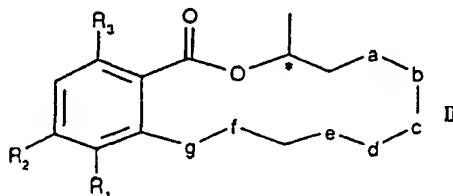
-f-g- is -CH₂-CH₂-, or cis or trans -CH=CH-,

or a pharmaceutically acceptable salt thereof or a physiologically-hydrolysable and -acceptable ester thereof.

ABSTRACTPHARMACEUTICAL USES

New pharmaceutical uses of radicicol analogs comprise use for the prophylaxis and treatment of cancers and/or malignant diseases, e.g. oncogene related cancers and malignant diseases.

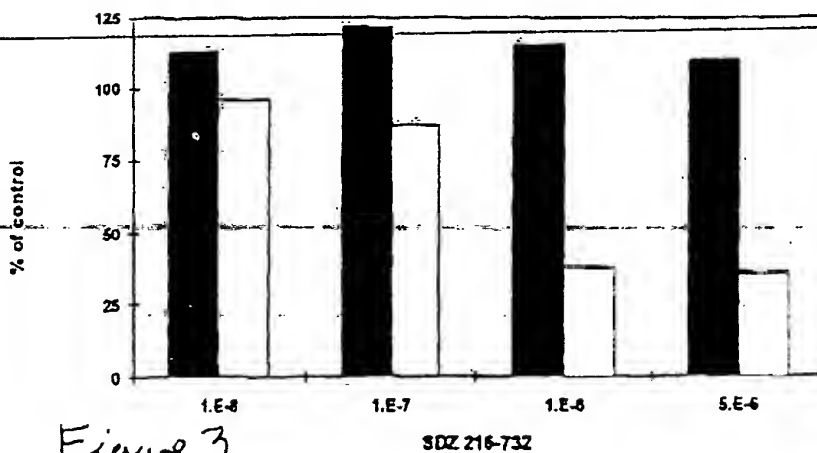
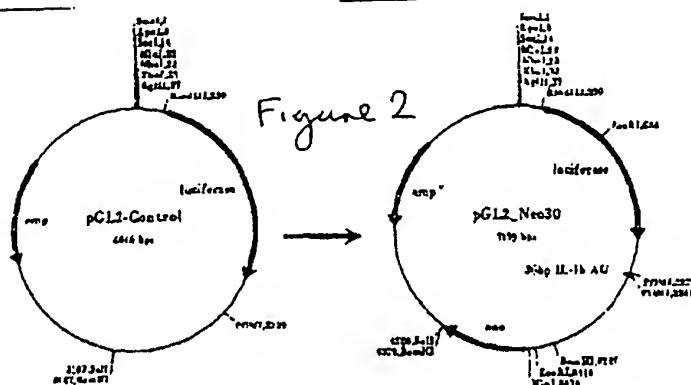
Preferred radicicol analogs for use in the invention comprise compounds of formula II



wherein the symbols are as defined.

ATGGCTTCCCTATTTATTTATTTATTTGTTTGTCCAACTT
 |||||
 GGATACCGAAGGGATAAATAAATAAATAAACAAACAGGTT

Figure 1





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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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